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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,548	12/01/1998	SURYA K. GOLI	PF-0233-1-DI	4355

27904 7590 01/17/2003

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/17/2003

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 28

Application Number: 09/203,548
Filing Date: 12/01/98
Appellant(s): Goli et al.

date mailed
01/17/03

P. Ben Wang
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 9-24-01 (paper No. 18).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect

or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct except for the last paragraph. There is no citation of page and line number from the specification for the last paragraph of the summary.

(6) Issues

The appellant's statement of the issues in the brief is correct except for item 2. Item contains the appellants' own paraphrase (e.g. in toxicology ...) of the rejection which is not part of the issues of the rejection because appellants are expressing their opinion and not stating the issues of rejection.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 18, 19, 33, and 34 do stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims

under appeal.

5,976,837 Jacobs et al. 11-1999

Friedberg et al. "Sequence of a novel cytochrome CYP2B cDNA coding for a protein which is expressed in a sebaceous gland, but not in liver." Biochem J., vol. 287 (1992), pp. 775-783.

Meyer et al. "Purification and partial sequencing of high-affinity progesterone-binding site(s) from porcine liver membranes." European J. Biochem., vol. 239 (1996), pp. 726-731.

Falkenstein et al. "Full-length cDNA sequence of a progesterone membrane-binding protein from procine vascular smooth muscle cells." Biochemical and Biophysical Research Communications, vol. 229 (1996) pp. 86-89.

Selmin et al. "Isolation and characterization of a novel gene induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rat liver." Carcinogenesis, vol. 17, no. 12 (1996) pp.2609-2615.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 18-19 and 33-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The claims are directed to a polypeptide comprising SEQ ID NO:1 and its variants in claim 18 limitations where the polypeptide is a receptor for which the function is not known. Although the closest prior art (Falkenstein et al.) teach that the protein binds progesterone, the protein is not the traditional progesterone steroid receptor which translocates to the nucleus which is well known. Rather the protein is only identified by binding characteristic which does not reveal its function. The specification as filed does not disclose or provide evidence that points to a property of the claimed receptor such that another non-asserted utility would be well established. Since the function of the protein is not known, the protein lacks well established utility. The specification on page 3 disclose the asserted utility of using the polypeptide in treating disorders associated with aberrant cellular development and differentiation and inflammation. However, there is no nexus between the unknown properties of the polypeptide and the treatment of the disease. Thus, the treatment of the disease lacks substantial utility because further research to identify or reasonably confirm a "real world" context of use is required. Any utility of the nucleic acid encoding the protein or other specific asserted utility is directly dependent on the function of the protein. A circular assertion of utility is created where the utility of the protein is needed to break out the circular assertion of utility. The claimed method using the polypeptide does not have well established utility because different polypeptide would have different functions and the skilled artisan would have to determine the function of the polypeptide. The claimed polypeptides do not substantial utility because the skilled artisan would need to prepare, isolate, and analyze the protein in order to determine its function and use. Therefore, the invention is not in readily available form. Instead, further experimentation of the protein itself would be required before it could be used. The disclosed use for the polypeptide of the claimed invention is generally

applicable to any polypeptide and therefore is not particular to the polypeptide claimed.

Claims 18-19 and 33-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 18 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 18 limitation (b) encompass a protein encoded by an allelic variant because of the recitation of a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1. Thus, claims encompass a subgenus of "naturally occurring allelic variants" which is not disclosed in the specification. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutation sites. However, the specification only discloses one subgenus of the human polypeptide. Furthermore, the species for the human is not known because some of the amino acids are represented by Xaa for any amino acids or unknown amino acids. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is they are variant structures and in the present state of the art the structure of one does not provide guidance to

the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Claims 18 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Friedberg et al.

Friedberg et al. disclose a CYP2B12 (pages 778-779, figures 3 and 6).

Claims 18 and 33 encompass a "biologically active fragment" and an "immunogenic fragment". Friedberg et al. disclose a CYP2B12 which has 4 amino acid sequence identical to SEQ ID NO:1. The buffers are pharmaceutically acceptable excipient.

Claims 18 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Meyer et al. as evidenced by Falkenstein et al.

Meyer et al. disclose the progesterone binding protein (Figures 1-4).

Falkenstein et al. disclose a porcine progesterone membrane binding protein (pages 86-89).

Claims 18 and 33 encompass a "biologically active fragment" and an immunogenic fragment. Meyer et al. protein inherently has the amino acid sequence taught by Falkenstein et al. Falkenstein et al. teach that the protein which has 93% amino acid sequence identical to SEQ ID NO:1. The buffers are pharmaceutically acceptable excipient.

Claims 18 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Jacobs et

al.(US 5,976,837).

Jacobs et al. disclose a porcine progesterone membrane binding protein and pharmaceutically acceptable excipient (columns 3-4, 14-15, 20-21, 23-24, and 39-40).

Claims 18 and 33 encompass a "biologically active fragment" and an immunogenic fragment. Jacobs et al. disclose a protein which has 93% amino acid sequence identical to SEQ ID NO:1.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Selmin et al. is cited as cumulative references with Falkenstein et al.

(11) Response to Argument

Claims 18-19 and 33-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Appellants argue that the rejections are based solely upon the unfounded assertion that the claimed polypeptide has no known function. However, appellants arguments concerning the function of the claimed polypeptide are not persuasive. Appellants argue in one case the claimed polypeptide has 79% sequence identity indicates that it is a 25-Dx protein which is responsive to dioxin in the liver and whereas in another case the claimed polypeptide has 93% sequence identity with a procine steroid membrane binding protein which binds progesterone found in vascular smooth muscle cells and thus concluding that the claimed polypeptide is the human membrane bound progesterone receptor. It should be noted that there is no nexus or relationship between 25-Dx protein and the progesterone binding protein functions. Dioxin is

a toxic compound whereas progesterone is a steroid hormone whose function is not related. It appears that the genus of this polypeptide has generic function which is separate for each protein. Furthermore, Falkenstein on page 86 in the next paragraph teach that this "protein is likely to represent the first putative steroid membrane receptor or a part of which sequence information is available." Thus, Falkenstein teaches that further experimentation is needed by using terms such as "likely" and "putative" and thus does not meet the substantial utility.

Appellants directs the examiner's attention to page 3 of the specification and reference of record, Wehling. However, page 3 of the specification discusses the relationship between the internal homology of 25-Dx, progesterone binding protein, and IL-6 and the nexus to the IL-6 related diseases. The percent identity of amino acid sequence between the progesterone binding protein to the claimed CYSTAR protein is different from the percent identity of amino acid sequence comparison between 25-Dx and claimed CYSTAR. The percent identity to IL-6 is even lower when compared to others. Yet the asserted utility of the claimed protein to IL-6 related diseases are made on page 3 of the specification. Furthermore, there is no relationship between page 3 of the specification and the reference of Wehling.

Appellants cite teachings from Wehling for a clear nexus between the function of CYSTAR and reproductive/developmental disorders. Appellants argue that the reference by Wehling on page 375 teach that progesterone was known to cause non-genomic actions including effects on oocyte maturation and the spermatozoan acrosome reaction. However, Wehling on page 375, last lines, teach that "the rapid nongenomic effect of progesterone on the spermatozoan acrosome reaction has been questioned recently and future research must delineate the conditions under which progesterone activates the acrosome reaction, if at all." Thus, Wehling teaching indicates that there is doubt as to the progesterone effect and need for

further experimentation which lacks substantial utility. Furthermore, the asserted utility on page 3 that "possible linkage between cytokine receptor-mediated signal transduction and steroid signaling pathways in the development of both neoplastic and inflammatory responses" lacks substantial utility because there is no nexus between the possible acrosome reaction of the sperm and IL-6 related diseases and asserted utility on page 3 of the specification.

Appellants discuss on pages 9 of the Brief the references of US patent 5,976,837(Jacobs et al.) as additional evidence of patentable utility but the reference has not been considered because the references does not comply with 37 CFR 1.195 for not showing good and sufficient reasons why the references were not earlier presented.

Appellants discuss on pages 10-11 of the Brief the asserted utility by using the references of Steiner et al., Rockett et al., and Nuwaysir et al. references with regard to practical uses of toxicology testing and drug development for the claimed invention, but the references have not been considered because the references does not comply with 37 CFR 1.195 for not showing good and sufficient reasons why the references were not earlier presented.

Applicants argue that CYSTAR has sufficient high homology to rat 25-Dx protein as to indicate substantial likelihood of similar function. However, the percent identity of amino acid sequence between CYSTAR and rat 25-Dx is much lower than CYSTAR percent identity of amino acid sequence comparison with progesterone binding protein. Furthermore, underlying the difference in structure is the different functions of progesterone binding protein and 25-Dx, since progesterone binding protein appears to bind progesterone while 25-Dx appears to be induced by dioxin, TCDD, but whose physiological function is not known. Thus, there is no nexus between the CYSTAR protein and rat 25-Dx protein in function since

the rat 25Dx is an orphan protein. No evidence has been provided that CYSTAR is responsive to dioxin or TCDD. Appellants further link homology to IL-6 receptor due to homology in the transmembrane receptor. However, there is no evidence that the claimed CYSTAR protein is related to interleukin-6 receptors in function. Appellants asserted utility for immune disorder requires the relationship between CYSTAR protein's unknown function and interleukin-6 receptor. However, since the CYSTAR protein is not known to bind interleukin-6 there is no nexus between the CYSTAR protein and interleukin-6. Furthermore, aside from the hydrophobic region the interleukin-6 receptor has very low homology with CYSTAR. Based on the overall divergent structure of CYSTAR and interleukin-6 receptor, the possible functional similarity between CYSTAR and interleukin-6 receptor seems remote. Substantially more research is required to understand to create a nexus between the claimed CYSTAR protein and to diseases. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Claims 18 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Appellants argue that clams at issue do not describe a genus which could be characterized as "highly variant" citing Brennar et al. as evidence. Appellants argue that Brennar et al. supports the premise that naturally occurring molecules may exist which could

be characterized as cytokine/steroid receptor proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. Thus, appellants argue that the claimed variation of 90% to the sequence of SEQ ID NO:1 differs far less than the 40% sequence identity suggested by Brennar et al. However, it should be noted that the percent identity measurement by Brennar et al. is correlated with "evolutionary homology" which cannot be functionally defined. Brennar et al. use already available database of sequence to identify sequences with "evolutionary homology", thus the technique cannot envision the sequence which would be allelic variant which is functional. Brennar et al. state on page 6075, "In practice, perfect separation is impossible to achieve so instead one is interested in drawing a threshold above which there are the largest number of related pares of sequences consistent with an acceptable error rate." Thus, even using statistical error rate analysis where there has to be assumption of parameters set forth on page 6074 of Brennar et al., the analysis cannot envision the allelic variant which has function. Interestingly, the claims are drawn to variants of an orphan receptor whose function cannot be explicitly defined. The best functional limitation of the claim is the regulation of expression of the protein by the species of dioxin. However, regulation of the expression is not per se regulated by the protein but rather by the inducer molecules and even if the protein was not functional or not related to the claimed protein the dioxin can regulate the expression of the protein. Since there is no limiting functional limitation, the genus is quite large especially for an orphan receptor whose function is not known. Furthermore, the claimed 5% variation is quite large - there are 22 known basic amino acid, which does not include the large numbers of analogues of the amino acids, that could substitute for each position where 11 amino acids (5%) out of 220 amino acid sequence can be simultaneously substituted. The factorial results of possibilities are beyond trillions.

Thus the genus is large and the computational programs cannot envision the allelic sequence until it has been isolated much in the same way in *Lilly* where human sequence could not be envisioned from the rat sequence. With regard to Xaa of unknown amino acids, it should be noted that many alleles are single amino acid changes and if the change is in the Xaa region which could not be sequenced then the allelic variant cannot be envisioned since the specification does not disclose the sequence necessary for comparison. Appellants argue that state of the art the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* application. However, the advancement in technology has not progressed to the state where one of skilled in the art can envision the allelic variant of CYSTAR which is functional without first identifying and sequencing the protein. The state of the art is such that one skilled in the art using any technique cannot envision even in a known functional protein the allelic variant which is functional in another species such that even if a sequence is known in a rat, the allelic variant cannot be predicted in human.

With regard to rejection of claims 18 and 33 under 35 U.S.C. 102(b) as being anticipated by Friedberg et al. and under 35 U.S.C. 102(a) as being anticipated by Meyer et al. as evidenced by Falkenstein et al., appellants argue the issues collectively together.

Appellants argue that the claimed immunologically active fragments generate antibodies that bind specifically to SEQ ID NO:1 and not to other polypeptides and thus the reference fragment cannot generate such antibodies since of necessity any antibodies generated by these fragments would also bind to the reference polypeptides. However, the term "specifically binds" is not defined in the specification as alleged by the appellants. Since any antibody generated with the reference polypeptide region which overlaps with the SEQ ID NO:1 will

have the same sequence the antibody will bind specifically to SEQ ID NO:1 over non-specific polypeptides such as albumin or non-specific binding of control assay which does not contain SEQ ID NO:1. One skilled in the art of antibody binding would determine in the assay the specific binding by comparing the assay binding with SEQ ID NO:1 versus the control assay of non-specific binding without the SEQ ID NO:1 which is the background binding. Thus, the antibody generated with the reference polypeptide would specifically bind to the SEQ ID NO:1.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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MDP
January 13, 2003

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